Summary

Two cases of recurrent exsanguinating menorrhagia following childbirth and miscarriage, which finally had to be subjected to hysterectomy, are described.

On pathological examination the cause for the severe uterine haemorrhages was found to be a surviving large-calibre vessel of the placental bed, possibly an arterial branch, which had failed to undergo involution in the normal way during the puerperium.

To the authors' knowledge this syndrome has not been described previously.

We would like to express our gratitude to Dr. R. Pollok for allowing us to include his case as Case 2 in this paper, and to Professor R. A. Willis for reading the manuscript. We are indebted to Miss Phyllis E. Coleman for the photography.

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HAEMOGLOBIN "SINGAPORE-BRISTOL"

A "FAST" HAEMOGLOBIN FOUND IN INFANTS

BY

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At a symposium on abnormal haemoglobins held in Istanbul in 1957, Fessas (1959a) described a "fast"-moving haemoglobin which he had seen in an infant but not in its parents. The component disappeared from the child's blood when it grew older. This observation was interpreted by Fessas as being possibly the first demonstration of an abnormal foetal haemoglobin. Further details were published by Fessas and Papaspyrou (1957). Also in 1957 Vella (personal communication) noted in Singapore that some cord bloods of Chinese infants contained a fast-moving haemoglobin which could not be demonstrated in the blood of either parent. Early in 1958 he sent specimens to Fessas in Athens and to us in London. Fessas considered that this haemoglobin variant was the same as that which had been seen by him and his colleagues in the Greek infant. At that time Ager and Lehmann (1958) investigated a haemoglobin found in an infant at St. Bartholomew's Hospital. This haemoglobin differed from that sent by Vella and from that described by Fessas and Papaspyrou (1957). It was decided to call this pigment haemoglobin "Bart's," and to refer to the other not yet named abnormal foetal haemoglobin as the "haemoglobin of Fessas and Papaspyrou" ("F & P").

The principal differences between the two haemoglobins were that Bart's moved on paper electrophoresis at alkaline pH in front of haemoglobin J, whereas F & P did not, and that Bart's was resistant to alkali denaturation in the "one-minute alkali denaturation test" of

Singer, Chernoff, and Singer (1951) and by other alkali-denaturation procedures, whereas F & P was denatured as haemoglobin A.

A difficulty in nomenclature arose in 1958 when Fessas (personal communication) found more cord bloods and bloods of infants with a fast-moving haemoglobin which had all the properties of haemoglobin Bart's, and was led to the conclusion in retrospect that the first example of an abnormal foetal haemoglobin seen by him in 1957 had also been of this type rather than of that which had meanwhile been referred to as F & P. Nevertheless, there existed undoubtedly two types of fast-moving haemoglobins in cord blood of infants whose parents showed no abnormal haemo-

FIG. 1.—Comparison of a haemoglobin A+J control (middle) with the haemoglobins of Case 1 (right) and Case 2 (left). The fast-moving component in Cases 1 and 2 moves slightly less fast than J. Electrophoresis on cellulose acetate with barbiturate buffer pH 8.6. Strip stained with light green.

globin, one moving on paper electrophoresis at pH 8.6 faster and one moving slower than haemoglobin J (Vella, 1959).

We here record observations on a haemoglobin variant seen in two families in the offspring but not in their parents, which moved on paper electrophoresis at pH 8.6 in front of and separating from haemoglobin A but behind the position occupied under this condition by haemoglobin J (Fig. 1).

Case 1.—B.B. presented with anaemia at the age of 2½ years (under the care of Professor C. B. Perry). The spleen could not be felt. The haemoglobin level was 7.4 g./100 ml., and the smear showed considerable hypochromia, anisocytosis, and target cells. There was a satisfactory response to treatment with iron by mouth. The haemoglobin was examined on three occasions, and each time showed a fast-moving component on electrophoresis on paper and cellulose acetate at pH 8.6. Alkali-resistant haemoglobin (Singer *et al.*, 1951) 5%. **Family:** Father of French, Portuguese, and East Indian extraction; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.7%. Mother English; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.7%.

Case 2.—E.T. presented with anaemia at the age of 2½ years (under the care of Dr. J. Apley). The spleen was enlarged three fingerbreadths. Haemoglobin level was 7.4 g./100 ml.; P.C.V., 31.5%; R.B.C., 4,400,000/c.mm.; M.C.V., 72 cubic microns; M.C.H.C., 26%. Serum iron 23 µg./100 ml.; serum bilirubin, 0.35 mg./100 ml. The tibial marrow was normoblastic, with evidence of iron deficiency.

The osmotic fragility of the red cells was normal (a slight "tail" at 0.35 to 0.2% NaCl, presumably due to leptocytosis). There was a satisfactory response to parenteral iron. The haemoglobin was examined on two occasions, and each time showed a fast-moving component on electrophoresis on paper and cellulose acetate at pH 8.6. Alkali-resistant haemoglobin 3%, 4%. *Family*: Father of Jamaican origin; his blood was obtained by the kind co-operation of Professor D. V. Hubble, of Birmingham; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 2.1%. Mother English; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.9%. Sister by the same father and the same mother, aged 1 year; had a mild microcytic anaemia; haemoglobin level was 11 g./100 ml.; M.C.V., 78 cubic microns; M.C.H.C., 31%; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 3.7%.

Properties of the Present Haemoglobin

Paper electrophoresis at pH 8.6	Moves between A and J (Fig. 2)
Paper electrophoresis at pH 6.5	No separation from A (Fig. 3)
Chromatography on "amberlite IRC 50" at pH 6	Separation in front of F but behind H (Fig. 4)
Alkali resistance of isolated fraction	Indistinguishable from A
Ultra-violet spectrum	Not clearly distinguishable from A

As regards the ultra-violet spectrum, results have not been uniform. On a few occasions a slope clearly of

FIG. 2.—Comparison of the Singapore cord blood with a sample of haemoglobin A+J. Paper electrophoresis at pH 8.6. Strip unstained. The fast-moving component in the cord blood moves slightly behind J.

FIG. 3.—Comparison between the cord haemoglobin from Singapore with haemoglobins A+F+Bart's and haemoglobin A+H. Paper electrophoresis pH 6.5. Strip unstained. The fast-moving haemoglobin in the Singapore sample does not separate from haemoglobin A.

FIG. 4.—Chromatography on amberlite IRC 50, pH 6, of the haemoglobin of Case 2. A compound is seen separating in front of the haemoglobin F fraction. The fraction is diffuse and therefore seems to be less in quantity than the F fraction. This is not actually so.

the foetal type was obtained—once on a specimen received from Dr. Vella (Singapore), and once on a specimen from Case 1. However, careful and repeated screening and repetition of ultra-violet spectrum curves failed to yield irrefutable confirmation of the earlier observations, though suggestive results were obtained (Fig. 5). If a foetal type of ultra-violet spectrum exists it must be of a very slight type which cannot be demonstrated with the same ease as that associated with haemoglobin F and haemoglobin Bart's.

The only indication that this variant may be an abnormal foetal haemoglobin is the similarity with haemoglobins F and Bart's, inasmuch as this compound is found in infants but not in parents; but there is no supporting evidence from the results of the alkali denaturation

FIG. 5.—Haemoglobin of Case 1. Ultra-violet spectrum of haemoglobin fractions eluted after starch electrophoresis at pH 8.6. A=Slow-moving component. B=Fast-moving component (haemoglobin Singapore-Bristol). A slight inflexion at 289.8 mμ; the region of the "foetal notch" is noticeable. This phenomenon was less definite in other samples.

test and the ultra-violet spectrum type which had been so decisive in the case of haemoglobin Bart's.

The variant described here differs from all hitherto described human haemoglobins excepting that observed by Vella (1959) and then referred to as the F & P type. There is even one difference from that described by the Greek authors: the present pigment does not separate from haemoglobin A on acid electrophoresis. Another pigment migrating on alkaline paper electrophoresis behind J and in front of A is haemoglobin K. Haemoglobin K, however, moves slightly slower than the pigment described here and does not separate from haemoglobin A on chromatography. We cannot be sure that the present haemoglobin is truly a variant of haemoglobin F. It could conceivably be a recessive character in the adult series. After consultation with Dr. Vella (Singapore), we have decided on the provisional designation haemoglobin "Singapore-Bristol."

Summary

Of two "fast" haemoglobins seen in infants, but not in their parents, one moves more slowly than haemoglobin J on paper electrophoresis at alkaline pH, and the other faster. The second has been described as haemoglobin "Bart's" and is now thought to be the unnamed abnormal foetal haemoglobin seen by Fessas and Papaspyrou in 1957 (Fessas, 1959b). The other moves more slowly than haemoglobin J, and two new examples in infants of mixed marriages are described. This pigment has previously been referred to as the haemoglobin of Fessas and Papaspyrou ("F & P"); it is now redesignated haemoglobin "Singapore-Bristol," and its properties are described.

ADDENDUM.—Two relevant reports have appeared since the above studies were completed. Virginia Minnich and her colleagues (1959) examined the cord blood of 200 infants (110 negroes and 90 Caucasian), and in nine of the negro babies and one of the Caucasians a fast-moving haemoglobin was found which moved more slowly than haemoglobin J on electrophoresis at alkaline pH. These authors state that they found this fraction to be relatively resistant to alkali denaturation, whereas we did not find this to be the case for haemoglobin Singapore-Bristol. Hendrickse and his colleagues (1960) found a "fast" haemoglobin fraction in 11% out of 100 cord bloods examined in Nigeria. This fraction persisted for only the first two months of life. Three were examined further, and one of them was found to resemble haemoglobin Bart's and two the haemoglobin described in the present paper.

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RESPONSE TO GLUCAGON BY SUBJECTS WITH HYPERINSULINISM FROM ISLET-CELL TUMOURS

BY

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The isolation and purification (Staub, Sinn, and Behrens, 1955) of glucagon—the hyperglycaemic-glycogenolytic factor—which contaminates many commercial preparations of insulin, enables its effects to be studied in man. Its exact physiological role in intact animals is still in doubt (*Lancet*, 1955; *Brit. med. J.*, 1956), but it is generally agreed that working in conjunction with insulin it facilitates glucose transport from the liver to the peripheral tissues and its utilization there (Anderson, Monaco, Perfetto, and Termine, 1957).

This paper records the results of administering glucagon to four subjects with hyperinsulinism.

Material and Methods

Glucagon, 1 mg. in 1 ml., was given by intramuscular injection in subjects in the postprandial state, about six to eight hours after the last meal. Glucose concentrations were measured in capillary blood before and at 5, 10, 15, 30, 45, 60, 120, and 150 minutes after the injection by a glucose-oxidase method (Marks, 1959).

Four subjects with organic hypoglycaemia from hyperinsulinism were studied in addition to normal subjects and patients suspected of hypoglycaemia but in whom the diagnosis was not substantiated. In three of the hypoglycaemic patients an islet-cell tumour was removed at operation. The fourth patient refused operation though the diagnosis of insulinism was not in doubt clinically.

Results

The results in normal subjects resemble those observed by others (Hubble, 1955; Alivisatos and

Response to 1 mg. of glucagon given intramuscularly in four subjects with hyperinsulinism from islet-cell tumour. The results from a typical normal individual are shown for comparison.